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EXAMINER
KERR, KATHLEEN M

ART UNIT	PAPER NUMBER
1652	

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13

Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Application No. 09/941,936	Applicant(s) BATHE ET AL.	
	Examiner Kathleen M Kerr	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *1-13 and 30-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Alignment* .

DETAILED ACTION

Application Status

1. In response to the previous Office action, a written restriction requirement (Paper No. 11, mailed on June 4, 2003), Applicants filed an election received on July 3, 2003 (Paper No. 12). Thus, Claims 1-32 are pending in the instant Office action.

Election

2. Applicant's election of Group III, Claims 14-29 in Paper No. 12 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (M.P.E.P. § 818.03(a)).

The requirement is still deemed proper and is therefore made FINAL. Claims 1-32 are pending in the instant application. Claims 1-13 and 30-32 are withdrawn from further consideration as non-elected inventions. Claims 14-29 will be examined herein.

Priority

3. The instant application is granted the benefit of priority for the foreign application 10043332.4 filed in Germany on September 2, 2000 and application 10033426.5 filed in Germany on July 10, 2001 as requested in the declaration. Receipt is acknowledged of papers (both foreign priority documents as noted above) submitted under 35 U.S.C. § 119(a)-(d), which papers have been placed of record in the file. Said papers are not in English.

Information Disclosure Statement

4. The information disclosure statement filed on April 8, 2002 (Paper No. 9) has been reviewed; its references have been considered as noted on the attached copy.

Reference "AI", the search report, has been considered, but crossed out since it is not printed on the face of any patent application.

Declaration

5. The declaration filed on December 14, 2001 has been accepted. It notes that the specification was "attached hereto"; however, this is incorrect since the specification was filed on August 30, 2001. This is clearly a typographical error and noted herein to clarify the record only. No action is required by Applicant.

Sequence Compliance

6. By virtue of the sequence listing filed on February 13, 2002 (Paper No. 8), the instant application now fully complies with the sequence rules.

Objections to the Specification

7. The specification is objected to because the title is not descriptive. A new title is required that is clearly indicative of the invention to which the elected claims are drawn (see M.P.E.P. § 606.01). The Examiner suggests the following new title:

---Methods for Producing Amino Acids in Coryneform Bacteria Using an Enhanced SigC Gene---

8. The Abstract is objected to for not completely describing the disclosed subject matter (see M.P.E.P. § 608.01(b)). It is noted that in many databases and in foreign countries, the Abstract is crucial in defining the disclosed subject matter, thus, its completeness is essential. The Examiner suggests the inclusion of the source species, *Corynebacterium glutamicum* for completeness. Additionally, the Examiner notes that the Abstract is confusing due to it discussion of attenuating the sigC gene to produce amino acids while the specification and the claims describe using an enhanced sigC gene for such purposes. Clarification and/or amendment are required.

9. The specification is objected to for being confusing. On page 7, paragraph [0026], the phrase "enzyme sigma factor C" is unclear as to what enzyme function this protein has. Limited description can be found in the specification and/or the art. Clarification is required.

Objections to the Claims

10. Claims 22 and 23 are objected to under 37 C.F.R. § 1.75 as being duplicate claims of one another and of Claim 14. The phrase "expression ... is enhanced" is unclear, but seems to mean more expression, i.e., overexpression. Thus, Claims 14, 22, and 23 are drawn to methods using coryneform with overexpressed sigC. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See M.P.E.P. § 706.03(k). Cancellation or amendment of duplicate claims is required.

11. Claim 27 is objected to under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The limitation of using only coryneform bacterium in Claim 14 is not further limited by requiring the bacteria to be from the genus *Corynebacterium* since this is the definition of the term coryneform.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 14-27 and 29 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "the sigC gene or nucleotide sequences coding for the latter" is unclear as to its metes and bounds. The specification discloses a single sequence defined as a sigC gene in SEQ ID NO:1, which encodes SEQ ID NO:2. This encoded protein is described as "an enzyme sigma factor C" on page 7 but no further explanation of this enzymatic activity is described in either the specification. The art contains a reference to sigC; however, the encoding DNA disclosed has no similarity to SEQ ID NO:1 (Amador *et al.* Microbiology (1999) 145:915-924). Thus, if the claims were drawn to using enhanced SEQ ID NO:1 or any DNA encoding SEQ ID NO:2, the metes and bounds would be clear. If the claims are drawn to enhancement using any sigC gene, without clear definition of a sigC gene, the claims are wholly unclear. Clarification is required.

13. Claims 15-16 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The added step in Claim 15 is unclear as to its intended claim limitation. The process steps on Claim 14 will enrich the medium with L-amino acid since coryneform naturally produce L-amino acids in culture. Is some particular level of enrichment required? The limitations are wholly unclear. Clarification is required.

14. Claims 19-20 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The metes and bounds of the cited "pathways" are unclear so that the skilled artisan would be unable to identify enhancement (or reduction) of which additional genes reads on the claims. The specification cites only examples of genes to be turned on or off and do not define the pathways. Since coryneform bacteria have integrated, complex pathways of biosynthesis and degradation, the particular nature of the intended additional genes is unclear without at least citation to a particular reference. Clarification is required.

15. Claims 22-23 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "expression ... is enhanced" is unclear as to its meaning if other than ---overexpression--- as in Claim 23. Clarification is required.

16. Claim 24 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as

the invention. The term "regulatory properties" of the sigC polypeptide is unclear. No such properties are described in the specification. Moreover, as noted above, no particular activity of the protein (enzyme) is noted so it would be wholly impossible for one of skill in the art to know what further "regulatory properties" since no activity can be assessed clearly. Clarification is required.

17. Claims 25-26 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In each claim's Markush group, the listed genes are shown as "**the** gene dapA" for example (emphasis added). It is unclear if this particular (as implied by the article "the") dapA gene is the dapA gene of the coryneform in which the method is being practiced or can any dapA gene, for example from *E. coli*, be overexpressed and meet the limitations of the claims? Clarification is required.

18. Claim 25 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "the gene lysE coding for lysine export" is unclear. Genes do not code for functions; genes codes for enzymes or proteins that have function. The appropriate phrase is ---the gene lysE coding for a protein for lysine export---. Correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

19. Claims 14-27 and 29 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 14 is drawn to methods of producing amino acids in coryneform having enhanced a sigC gene, wherein sigC is claimed solely by function and without any structural limitations.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

In the instant specification, the sigC gene is described as encoding "an enzyme sigma factor C" on page 7 but no further explanation of this enzymatic activity is described in either the specification or the art. A single example of a sigC protein is described in SEQ ID NO:2, but no indication of how this structure is related to the noted function (albeit an unclear function).

Thus, one of skill in the art would be unable to predict the structure or function of other members of this genus by virtue of the instant disclosure. Therefore, claims drawn to methods using coryneform bacteria containing the genus of said genes are not adequately described.

20. Claims 14-17, 19-22, and 24-29 are rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for methods using coryneform bacteria with overexpressed sigC and/or amino acid biosynthetic genes and with deleted amino acid reduction genes, does not reasonably provide enablement for methods using bacteria with enhancement and/or switching off or attenuation of such genes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. To produce bacteria for use in the claimed methods to the full extent of the claimed scope would require undue experimentation.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of

experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

The instant specification describes enhancement as increasing the copy number of a gene, using a strong promoter, or using a corresponding gene coding for an enzyme with a higher activity (see page 6, paragraph [0022]). While the skill of the art enabled enhancement by overexpression, which would include increasing the copy number and using a strong promoter, of the disclosed sigC gene, no such enablement for using a corresponding gene coding for an enzyme with higher activity is found in the art. Furthermore, no activity of sigC is even known so that it can be increased using an altered protein form. The amino acid sequence of a sigC protein with higher activity is wholly unpredictable since no description of how the structure, SEQ ID NO:2, related to the function (albeit an unclear function). Thus, while the specification enables overexpression of the sigC gene (overexpression including means of art such as stronger promoters and increased copy number), it does not enable enhancement of said gene.

Similarly, the specification mentions in passing genes of the biosynthesis pathways of desired amino acids. The art contains numerous recitations of such genes and their enhancement by means of overexpression and alternate enzyme (more active enzyme) forms. The claims are enabled for such enhancements. However, where a more active enzyme form is not known in the art, such a form is wholly unpredictable from the art and the lack of any particular description in the instant specification.

Additionally, the "switching off" of biosynthetic pathways is a very complex procedure due to the intertwining of the multitude of biochemical pathways in coryneform. The specification enables methods that wholly delete said pathways so that the pathways are "switched off". Moreover, the specification enables methods using bacteria with deleted PEP carboxykinase genes (for example, as in Claim 26). However, the specification does not enable for alteration of the pathways so that they no longer reduce the formation of the desired amino acid using any means short of full deletion. Moreover, the specification does not enable attenuation of PEP carboxykinase, for example, by means other than deletion. The art contains numerous recitations of such pathways and genes and their reduction by means of deletion and alternate enzyme (less active enzyme) forms. The claims are enabled for such reduction or attenuation methods. However, where a less active enzyme form is not known in the art, such a form is wholly unpredictable from the art and the lack of any particular description in the instant specification.

21. Claim 24 is rejected under 35 U.S.C. § 112, first paragraph, enablement, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Raising the regulatory properties of a sigC polypeptide for use in the claimed methods would require undue experimentation. The factors to be considered in determining whether undue experimentation is required are summarized above.

Not only are regulatory pathways of the sigC polypeptide not described in the specification or known in the art, but also the normal activity of sigC polypeptides is not

described. Without any indication of function, it is wholly unpredictable how a skilled artisan would be able to regulate such an activity. No guidance or working examples are offered in the instant specification. The state of the art is totally devoid of discussion of sigC polypeptide regulation. Thus, the instant claim is not enabled.

22. Claim 25 is rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for methods using known feedback-resistance aspartate kinase and threonine dehydratase, does not reasonably provide enablement for methods using unknown feedback-resistance aspartate kinase and threonine dehydratase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Identifying novel feedback-resistance aspartate kinase and/or threonine dehydratase polypeptides for use in the claimed methods would require undue experimentation. The factors to be considered in determining whether undue experimentation is required are summarized above.

The specification provides a single example of each of the named polypeptides but provides no guidance for the identification of new ones. The state of the art is such that a finite number of feedback-resistant aspartate kinases and threonine dehydratases are known; these are enabled. However, the predictability of finding other feedback-resistant aspartate kinases and threonine dehydratases is minute. Thus, the instant claim is not enabled to the full extent of its scope.

23. Claims 28-29 are rejected under 35 U.S.C. § 112, first paragraph, enabling deposit, as containing subject matter which was not described in the specification in such a way as to enable

one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. To practice the instant methods, one of skill in the art is required to use DH5αmcr/pEC-XK99EsigCb2ex or DSM5715/pEC-XK99E. While the instant specification contains limited deposit information on page 19, the requirements to enable such a deposit have not been fully met by the instant application. To enable the instant claims by enabling the deposit of DSM 12968, the following items are required: (1) the accession number assigned by the depository, (2) the date of deposit, (3) a brief description of the deposit, (4) the name and **full address** of the depository (37 C.F.R. § 1.801 - 1.809) (those which are in bold have not been fulfilled by the instant specification), **and (5)** the record must also contain a statement certifying that all restrictions on accessibility to said deposit be irrevocably removed by Applicant upon the granting of the patent (see M.P.E.P. § 2404.01); this statement may be certified by Applicants or Applicants' representative.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

24. Claims 14-18, 21-23, and 27 are rejected under 35 U.S.C. § 102(b) as being anticipated by Kimura *et al.* (EP 0864654). The instant claims are drawn to methods of making lysine using coryneform bacteria that overexpress, via a plasmid vector, sigC and further isolating said lysine.

Kimura *et al.* teach methods of making amino acids, particularly lysine, by overexpression of a gene encoding the sigma factor (see abstract and page 3, line 14). Without further clarity of the function of sigC in the instant specification, sigC is considered a sigma factor. Kimura *et al.* teach using plasmids in the methods (see page 6, example 1). Kimura *et al.* also teach coryneform as microorganisms for the disclosed methods (see page 3, line 22) and teach collection of the lysine by known methods (see page 5, lines 49-51).

25. Claims 14-18, 21-23, and 27 are rejected under 35 U.S.C. § 102(b) as being anticipated by Nakagawa *et al.* (EP 1108790, see IDS). The instant claims are drawn to methods of making lysine using coryneform bacteria that overexpress, via a plasmid vector, sigC and further isolating said lysine.

Nakagawa *et al.* teach methods of producing amino acids using transformants overexpressing all of the disclosed open reading frames therein and isolating said amino acids; they further teach *C. glutamicum* as host cells in said method (see page 4). Nakagawa *et al.* also teach lysine as preferred product of *Corynebacterium glutamicum* (see page 2). Nakagawa *et al.* teach a particular open reading frame similar to sigE in *M. smegmatis* that comprises a polynucleotide that is identical to the encoding portion of SEQ ID NO:1 (see page 49 and attached alignment); thus, Nakagawa *et al.* teach their methods using Applicants' sigC gene.

The Examiner notes that the publication date of Nakagawa *et al.* (June 20, 2001) does not pre-date Applicants' priority document DE 10043332.4. A translation of this document into English may afford this earlier filing date to the instant claims and overcome the instant rejection.

Conclusion

26. Claims 14-29 are not allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (703) 305-1229. The examiner can normally be reached on Monday through Friday, from 8:30am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (703) 308-3804. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

KMK
September 20, 2003